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Childhood Leukemia and Pesticides

In this issue, Infante-Rivard *et al*[1] investigate whether perinatal exposure to pesticides is related to childhood acute lymphoblastic leukemia, and whether genetic metabolic polymorphisms modify the risk. In the population-based case-control component of the study, several broad groups of pesticide products were associated with increased relative risks ranging from approximately 1.4 to 3.0, with odds ratios generally less than 2.0. For herbicides, plant insecticides, and pesticides for trees, odds ratios increased with the frequency of use to approximately threefold or fourfold for maternal use more than five times during pregnancy, but there were few subjects in the top exposure categories. In the case-only genetic component of the study, gene-pesticide interaction odds ratios were increased approximately fivefold among cases with the CYP1A1m1 and with the CYP1A1m2 mutation for some indoor insecticides, but not for other tested genotypes or other pesticides products. How strong is the evidence for the association between pesticides and childhood leukemia based on the case-control component of the study? How should we interpret the large interaction odds ratios from the case-only genetic component of the study? Do these apparent gene-environment interactions provide further support for the carcinogenicity of pesticides among children?

Leukemia has been linked to occupational pesticide exposure among adults, particularly farmers.[2] Two recent reviews of almost 2 dozen studies of childhood leukemia support a possible role for pesticides in childhood leukemia[3,4] Many, but not all, studies reported elevated risks of leukemia among children whose parents were occupationally exposed to pesticides or who used pesticides in the home or garden. Although the research has been limited by nonspecific pesticide exposure information, small numbers of exposed subjects, and potential for recall bias, the magnitude of the risks have often been greater than among adults, suggesting greater susceptibility.

The new study by Infante-Rivard *et al*[1] has several methodologic features that are improvements over earlier studies. First, the study has almost 500 cases, making it one of the largest studies of acute lymphoblastic leu-

kemia to address the risk associated with pesticide exposure. Second, the study is restricted to one leukemia cell type, whereas some studies have combined a variety of cell types, which may differ in their association with pesticides. Infant leukemia, which is thought to differ from leukemia among older children, was included, but these cases represent less than 3% of the study population. Third, the controls were selected from Canadian family allowance files, a near complete register of children in Canada.

The subjects' mothers were asked about pesticide use in the home by the type of pest(s) being eliminated and about pesticides used in the yard, garden, or for house plants by the specific purpose. Information was also collected on professional treatment of homes with insecticides and on use of insecticide products for pets or other domestic animals. The degree of detail in the pesticide use data exceeded all but a few of the earlier childhood leukemia studies. Individual pesticide names were not asked, but classes of chemicals could be inferred in a general way from the reported pests and product types, based on regional and national surveys of pesticide use. This inference was a nice addition, but these data, like many in other studies of general population exposures, still fall short of the detailed information on chemicals that can usually be obtained from farmers or other occupational groups, and that is needed to identify specific agents against which preventive action should be taken. It should be remembered, however, that crude exposure assessment with nondifferential exposure misclassification generally dilute risk estimates.

The exposure frequency and timing (that is, from 1 month before pregnancy to birth and from birth to diagnosis) were ascertained and evaluated. Identification of time periods of higher risk might provide insight into mechanism and causality; however, typically most exposed subjects are exposed during both time periods. In this study, there was some suggestion that use of herbicides, plant insecticides, and products for trees during pregnancy was associated with higher risk than use during childhood.

Similarly, most exposed subjects had contact with multiple pesticide products. In an attempt to disentangle the effects of individual products, persons exposed to only one agent or group of agents were evaluated separately. Generally, risks were not as elevated as in the analyses based on all exposed subjects. Even with the relatively large sample size in this study, however, there were few subjects with single exposure scenarios.

The vexing problem of recall bias, or case response bias, remains a possibility in this study. Mothers of leukemia cases may have anxiously pondered possible reasons for their child's disease and reported exposures that mothers of healthy children, who have not been vigorously examining their past exposures, may have failed to remember and report. False positive associations may thus have arisen; however, there was variation in the odds ratios for different pesticide groups, with some odds ratios less than unity, so a generalized overreporting by case mothers did not occur. Clearly, research on the effects of pesticides on childhood cancer needs either prospective collection of detailed exposure information, such as that reported by farmers in the Agricultural Health Study being conducted by the National Cancer Institute in collaboration with the National Institute of Environmental Health Sciences, Environmental Protection Agency, and the National Institute for Occupational Safety and Health,[5] or methodologic work to evaluate the magnitude of recall bias, if any, in this research.

The case-only genetic component of the study by Infante-Rivard *et al*[1] is based on 123 cases, although the numbers of exposed cases unfortunately were not provided for the genetic analyses. As is increasingly common in epidemiology, the presence of gene-environment interactions was evaluated despite lack of evidence for a main effect of the environmental exposure. The rationale is that the environmental exposure may only exert its effect in conjunction with a specific genetic metabolic polymorphism. It is certainly reasonable to consider gene-environment interactions in pesticide carcinogenesis, because genetic differences exist in the ability to metabolize pesticides. For example, among adults, at least a 15-fold difference in the ability to detoxify organophosphate insecticides has been observed.[6] A family history of cancer, a crude measure of genetic susceptibility, has appeared to enhance the carcinogenic effects of pesticides in case-control studies of adult leukemia and lymphoma,[7,8] although interpretation of these data is difficult.

On the one hand, some pesticide exposure categories associated with increased risk in the case-control component of the study were also associated with higher interaction odds ratios. For example, use of pesticides against mites and spiders during pregnancy was associated with an odds ratio of 1.4 in the case-control component and an interaction odds ratio of 5.0 for CYP1A1m1. The case-only component assumes that the genotype and exposure are independent in the population, which is reasonable, and cannot be affected by recall bias, because the case genetic status was unknown to the mother when reporting exposure.

On the other hand, an interaction odds ratio of 5.6 was reported for use of repellents and sprays during pregnancy among CYP1A1m1 cases, even though this exposure was associated with a deficit of risk (odds ratio = 0.7) in the case-control component. The relatively high prevalence of the allele (26%) suggests that use of repellents and sprays would be protective for children without the allele and a risk factor for children with the allele. The data require a strong qualitative interaction. It is unclear what the biologic basis would be for such a qualitative interaction, suggesting that the observed interaction odds ratio is more probably owing to chance. The main effect odds ratio for use of repellents and sprays during pregnancy among the controls and the subgroup of cases with genotype data would help to evaluate this finding.

More information on the main effects of the alleles on childhood acute lymphoblastic leukemia is also needed

to help interpret the interaction odds ratios. There has not been extensive work on this association to date, and what exists is inconclusive. Krajinovic *et al*[9] reported that risk of childhood acute lymphoblastic leukemia was positively associated with CYP1A1m2A, negatively associated with CYP1A1m4 in girls, and had no relation to other alleles. In another report, CYP1A1m2 alleles were not associated with infant leukemia.[10] Also, there is very limited evidence to date that these specific alleles have any relation to pesticide metabolism. In any event, this paper is one of the first, if not the first, to evaluate gene-environment interactions for pesticides and childhood leukemia, so the evidence must be viewed as preliminary.

Exposure assessment has been the Achilles heel of environmental epidemiology and continues to be. This study is a step above previous research on general population exposure to pesticides, but exposure measurement was still very imprecise. Ironically, genetic parameters can be measured with much more precision, but their meaning is unclear, particularly in case-only analyses of exposures for which the main effect is not well established. We continue to need improvements in exposure assessment, resolution of the nagging issue of recall bias, and further study of gene-environment interaction to understand better the effects of pesticide exposures on leukemia risk, particularly in susceptible populations.

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